Acute Kidney Injury in the Intensive Care Unit: Risk Factors and Outcomes

A dissertation submitted in partial fulfillment of
M.D (General Medicine) Examination of the
Tamil Nadu Dr. M.G.R. Medical University, Chennai to
be held in April 2011

CERTIFICATE

This is to certify that the dissertation entitled “Acute Kidney Injury in the Intensive Care Unit- Risk Factors and Outcomes” is the bonafide original work of Dr Shalom Solomon Patole towards the MD Branch I (General Medicine) Degree Examination of the Tamil Nadu Dr M G R Medical University Chennai to be conducted in March 2010

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ACKNOWLEDGEMENT

I thank God, for giving me the privilege of studying the beautiful subject of Medicine in this prestigious college and the honor of working under my guide Dr. George John and learning the art and science behind the scientific inquiry of a problem and the process of trying to answer it. Dr. John has been a source of valuable suggestions, and meticulous guidance, support and encouragement in doing this study and his experience has been invaluable. Its thanks mainly to him that this study was conceptualized and carried out and I don't think it would have been possible without him. This study would not have come into being without the expert guidance of Dr J. V. Peter who played a vital role in conceptualizing and planning the study. I am grateful to Dr Dilip Mathai, Dr. Kurien Thomas, Dr. O.C. Abraham, Dr. Thambu David, Dr. Priscilla Rupali, and the staff of the Department of General Medicine for the support received during the conduct of the study. I would also like to thank the doctors and the staff of the Medical ICU and HDU for their help.

Thanks are also due to Mrs. Grace Rebekah and Mr. Prasanna from the Department of Biostatistics for assistance in statistical analysis.

My wife Betsy and my parents have been the source of immense support, encouragement, prayers and assistance during this endeavor. My sincere gratitude to them. I would also like to thank my friends, and colleagues for their encouragement and assistance as well.

The cooperation and support of all my patients and their relatives have been crucial in the conduct of the study – and for this I am truly thankful to each of them.

INTRODUCTION

Acute Renal Failure (ARF) has traditionally been defined as the abrupt loss of kidney function that results in the retention of urea and other nitrogenous waste products and in the dysregulation of extra cellular volume and electrolytes. (1)The loss of kidney function is most easily detected by measurement of the serum creatinine which is used to estimate the glomerular filtration rate (GFR).

ARF can be asymptomatic or present with features of azotemia and oliguria or anuria and is diagnosed when biochemical monitoring of hospitalized patients reveals a new increase in blood urea and serum creatinine concentrations. ARF, as opposed to chronic renal failure is often considered to be reversible, although a return to baseline serum creatinine concentrations post injury might not be sufficiently sensitive to detect clinically significant irreversible damage that may ultimately contribute to chronic kidney disease(1).

Its incidence in the ICU in various studies is shown to be around two thirds of number of admitted patients (which makes it comparable to the incidence of acute lung injury (ALI) and severe sepsis), while 4–5% of ICU patients will require some form of renal replacement therapy (RRT) (1). The incidence of ARF is increasing with a higher mortality in those who have more severe renal dysfunction. Even patients who have received dialysis have a mortality of 40-50% (1).

This study was done to evaluate the risk factors for ARF in a developing country as most published studies done so far have been done from developed countries.

LITERATURE REVIEW

A survey as reported in a recent journal quoted more than 35 definitions in literature for ARF (1). ARF is found commonly in ICUs (Intensive Care Units). Various studies in tertiary centers quote figures ranging from 1% to 67% with mortality ranging from 20% to 40% (1). The commonest factors for the same being sepsis and hypovolemia, ARF is found to be as common as severe sepsis and ALI (Acute Lung Injury). ARF is found to induce incremental involvement of the coagulation pathway, the lungs and the central nervous system.

DEFINTIONS OF ACUTE KIDNEY INJURY (AKI):

The term Acute Renal Failure was first introduced by Homer. W. Smith in his textbook (2). Unfortunately, a precise biochemical definition of this term does not exist. The occurrence of azotemia and oliguria is actually a physical response to renal injury and may actually express a normally functioning kidney trying to maintain homeostasis. Conversely, a hypovolemic person with a normal urine output, actually may have a more pathological kidney (3). Thus, the traditional term, ARF, does not define a specific pathological state nor does it clearly define a clear cut criteria beyond which one can confidently say that a person has a malfunctioning kidney. In addition, there is no clear cut identification of acute tubular necrosis or pre renal failure.

Creatinine values and presence or absence of oliguria/ anuria was used in the assesment of renal function. The problems are associated with the use of the serum creatinine to quantitatively define ARF are as follows:

- Serum creatinine does not accurately reflect the GFR in a patient who is not in steady state. In the early stages of severe acute renal failure, the serum creatinine may be low even though the actual (not estimated) GFR is markedly reduced since there may not have been sufficient time for the creatinine to accumulate.

- Creatinine is removed by dialysis. As a result, it is usually not possible to assess kidney function by measuring the serum creatinine once dialysis is initiated. One exception is when the serum creatinine continues to fall on days when hemodialysis is not performed indicating recovery of renal function.

- Numerous epidemiologic studies and clinical trials have used different cut-off values for serum creatinine to quantitatively define ARF (4).

The lack of consensus in the quantitative definition of ARF has hindered clinical research since it confounds comparisons between studies. Some definitions employed in clinical studies have been extremely complex with graded increments in serum creatinine for different baseline serum creatinine values (3,4,5). As an example, in a classic study of the epidemiology of hospital-acquired acute renal failure, ARF was defined as an increase in serum creatinine of 0.5 mg/dL if the baseline serum creatinine was ≤1.9 mg/dL, an 1.0 mg/dL increase in serum creatinine if the baseline serum creatinine was 2.0 to 4.9 mg/dL, and a 1.5 mg/dL increase in serum creatinine if the baseline serum creatinine was ≥5.0 mg/dL (4).

The Acute Dialysis Quality Initiative (ADQI) was created by a group of expert intensivists and nephrologists to develop consensus and evidence based guidelines for the treatment and prevention of acute renal failure (5). Recognizing the need for a uniform definition for ARF, the

ADQI group proposed a consensus graded definition, called the RIFLE criteria (6). A modification of the RIFLE criteria was subsequently proposed by the Acute Kidney Injury Network, which included the ADQI group as well as representatives from other nephrology and intensive care societies.(5,6,7,8)

In view of these deliberations, the term acute kidney injury (AKI) was proposed to represent the entire spectrum of acute renal failure.

RIFLE CRITERIA: The RIFLE criteria consists of three graded levels of injury (Risk, Injury, and Failure) based upon either the magnitude of elevation in serum creatinine or a decrease in urine output, and two outcome measures (Loss and End-stage renal disease). The RIFLE strata are as follows (5,6,9):

- Risk — 1.5-fold increase in the serum creatinine or GFR decrease by 25 percent or urine output <0.5 mL/kg per hour for six hours

- Injury — Twofold increase in the serum creatinine or GFR decrease by 50 percent or urine output <0.5 mL/kg per hour for 12 hours

- Failure — Threefold increase in the serum creatinine or GFR decrease by 75 percent or urine output of <0.5 mL/kg per hour for 24 hours, or anuria for 12 hours

- Loss — Complete loss of kidney function (e.g., need for renal replacement therapy) for more than four weeks
- ESRD — Complete loss of kidney function (e.g., need for renal replacement therapy) for more than three months

The RIFLE criteria has correlated with outcome (mortality) in a number of studies (10,11,12,13,14,15,16).

A systematic review of 13 studies demonstrated a stepwise increase in the relative risk of death inpatients who met the RIFLE criteria for various stages of AKI (16). Compared to patients who did not have AKI, patients in the RIFLE stages of "risk," "injury," and "failure" had increased relative mortality risks of 2.4 (CI 1.94-2.97), 4.15 (CI 3.14-5.48), and 6.37 (CI 5.14-7.9).

Despite significant heterogeneity among studies, results from most individual reports were qualitatively similar.

Limitations: There are several important shortcomings to the RIFLE criteria:

- The "risk," "injury," and "failure" strata are defined by either changes in serum creatinine or urine output. The assignment of the corresponding changes in serum creatinine and changes in urine output to the same strata are NOT based on evidence. In the one assessment of the RIFLE classification that compared the serum creatinine and urine output criteria, the serum creatinine criteria was a strong predictor of ICU mortality, whereas the urine output criteria did not independently predict mortality (14). Thus, if the RIFLE classification is used to stratify risk, it is important that the criteria that result in the least favorable RIFLE strata be used (5).

- As mentioned above, the change in serum creatinine during acute renal failure does not directly correlate with the actual change in glomerular filtration rate, which alters the assignment of that patient to a particular RIFLE level. As an example, in a patient with an abrupt decline in renal function in the setting of severe ARF, the serum creatinine might rise from 1.0 to 1.5 mg/dL (88.4 to 133 micromol/L) on day one, 2.5 mg/dL (221 mmol/L) on day two, and 3.5 mg/dL (309 micromol/L) on day three.

  According to the RIFLE criteria, the patient would progress from "risk" on day one to "injury" on day two and "failure" on day three, even though the actual GFR has been <10

mL/min over the entire period. This issue is intrinsic to any assessment of acute renal failure based upon the serum creatinine level.

- It is impossible to calculate the change in serum creatinine in patients who present with ARF but without a baseline measurement of serum creatinine. The authors of the RIFLE criteria suggest back-calculating an estimated baseline serum creatinine concentration using the four-variable MDRD equation, assuming a baseline GFR of 75 mL/min per 1.73 sq.m (5). However, this approach has not been prospectively validated.

AKIN CRITERIA: Given these limitations, a modification of the RIFLE criteria has been proposed by the Acute Kidney Injury Network (AKIN). The AKIN proposed both diagnostic criteria for ARF and a staging system that was based on the RIFLE criteria (5,6,7,8) . In addition, the term acute kidney injury (AKI) was proposed to represent the entire spectrum of acute renal failure.

Diagnostic criteria : The proposed diagnostic criteria for ARF are an abrupt (within 48 hours) absolute increase in the serum creatinine concentration of ≥0.3 mg/dL (26.4 micromol/L) from baseline, a percentage increase in the serum creatinine concentration of ≥50 percent, or oliguria of less than 0.5 mL/kg per hour for more than six hours . The latter two of these criteria are identical to the RIFLE "risk" criteria. The addition of an absolute change in serum creatinine of ≥0.3 mg/dL is based on epidemiologic data that have demonstrated an 80 percent increase in mortality risk associated with changes in serum creatinine concentration of as little as 0.3 to 0.5 mg/dL (17). Including a time constraint of 48 hours is based upon data that showed that poorer outcomes were associated with small changes in the creatinine when the rise in creatinine was observed within 24 to 48 hours (18,19).

Two additional caveats were proposed by the AKIN group:

- The diagnostic criteria should be applied only after volume status had been optimized.
- Urinary tract obstruction needed to be excluded if oliguria was used as the sole diagnostic criterion.

A flaw with the last caveat is that, according to the current definition, AKI would still be used to describe the patient with acute urinary tract obstruction and an acute increase in serum creatinine. It is not clear whether the AKIN modifications to RIFLE have substantively changed the classification of patients with AKI or improved its ability to predict hospital mortality (20).

***Staging system*:** The classification or staging system for ARF is comprised of three stages of increasing severity, which correspond to risk (stage 1), injury (stage 2), and failure (stage 3) of the RIFLE criteria. Loss and ESRD are removed from the staging system and defined as outcomes.

The clinical applicability of these staging systems is still uncertain. However, they will likely have some utility in standardizing the definitions for epidemiologic studies and for establishing inclusion criteria and endpoints for clinical trials.

Ultimately it is hoped that these definitions will be replaced by more sensitive and specific biomarkers of renal injury. The use of such biomarkers, analogous to troponin as a marker of myocardial injury, will permit development of a new paradigm for classifying acute kidney injury that is not solely dependent upon serum creatinine or other functional markers.

CLINICAL UTILITY:

The RIFLE and AKIN criteria have helped to focus attention that decrements in renal function that result in small changes in serum creatinine concentration are associated with significant clinical consequences. However, the precise clinical utility of these criteria is uncertain. There is also an inherent confusion within these criteria as to whether prerenal and obstructive etiologies of ARF are subsumed in or are external to the definition of AKI (17).

These criteria have greatest utility in epidemiologic studies and in defining consistent inclusion criteria and/or endpoints for clinical studies.

EPIDEMIOLOGY OF ACUTE KIDNEY INJURY

AKI occurs in approximately 67% of patients admitted to the intensive care unit (1) and is commonly associated with multiple organ dysfunction syndrome (MODS). A decade ago, AKI was thought to be a benign entity that could be managed easily with supportive care and dialysis. It is now known that it has a significant negative impact on patient morbidity and mortality. Although epidemiologic data clearly demonstrates that acute kidney injury is independently associated with increased mortality, the mechanisms by which acute kidney injury causes death remain unclear. One explanation for the increased mortality is that acute kidney injury causes deleterious systemic effects including injury to other organs (21).

In India, a study done in an ICU in a tertiary care hospital showed that ARF (acute renal failure) was seen in 3.79% of cases in the ICU and associated with poor prognosis.

Presence of sepsis, MOSF, higher APACHE – II scores and ventilation need were correlated with higher mortality in ARF patients in the intensive care unit (22).

ETIOLOGY OF AKI:

The etiology for AKI in ICUs has been extensively studied. Some of the well known etiologies of the same are sepsis (23), diabetes (24), age (24), hypotension(25), hypovolemia (25), contrast administration (26), nephrotoxic drugs (27) , mechanical ventilation (28) and number of days (28) for which ventilation was done.

i) Age and Gender: The elderly population is more prone to acute kidney injury (AKI) than younger populations. Older patients have less renal reserve because of reduced glomerular filtration rates due to anatomic/functional changes, and concomitant diseases such as hypertension, diabetes, atherosclerosis, heart failure, ischemic renal disease, and obstructive uropathy. The risk of AKI may also increase as a result of aggressive diagnostic and therapeutic procedures, which include medical agents, radiology, and surgical intervention. AKI in the elderly has a multifactorial pathophysiology due to different etiologies. Studies that have specifically compared prognosis of AKI in elderly versus young over the recent years suggest that age is a predictor of long-term outcome (29). Gender is also found to be a separate risk factor in patients with AKI. Studies have shown that men are more susceptible to develop AKI as compared to women (30,31). The exact cause has not been discovered, but benign prostatic hypertrophy (BPH) could be a factor (31).

ii) Co morbidities: As age increases there is an increase in associated co morbidities associated with these patients. Common among these are diabetes, hypertension, along with associated complications of these like CKD, IHD. Studies done on patients in ICU with AKI have shown diabetics to be at a greater risk in developing AKI. The primary cause is a reduction in glomerular filtration rate (GFR) as diabetic nephropathy progresses, making patients susceptible to contrast induced AKI and hypovolemia. Also co existing disorders like atherosclerosis could further

compromise renal function especially if there is any trauma or surgeries where there is manipulation of the aorta is involved (31).

iii) Sepsis and MODS: Fever or hypothermia, leukocytosis or leukopenia, tachypnea, and tachycardia are the cardinal signs of the systemic inflammatory response syndrome (SIRS). SIRS may have an infectious or a noninfectious etiology. If an infectious etiology is proven then the patient is said to have sepsis (32). This can result in the multiple organ dysfunction syndrome (MODS) which is defined as the dysfunction of more than one organ, requiring intervention to maintain homeostasis (32). The pathology of sepsis and MODS has been postulated to be due to:

a) *Inflammatory response* via inflammatory mediators leading to a cascade mechanism in the body causing a systemic inflammatory response syndrome. The hallmark of septic shock is a decrease in peripheral vascular resistance that occurs despite increased levels of vasopressor catecholamines. Before this vasodilatory phase, many patients experience a period during which oxygen delivery to tissues is compromised by myocardial depression, hypovolemia, and other factors. During this "hypodynamic" period, the blood lactate concentration is elevated, and central venous oxygen saturation is low. Fluid administration is usually followed by the hyperdynamic, vasodilatory phase during which cardiac output is normal (or even high) and oxygen consumption is independent of oxygen delivery. This is one of the postulated mechanisms via which the SIRS can lead to MODS i.e. the global hypovolemia leading to a tissue ischemia and hypoxia.

b) Another mechanism postulated is that of apoptosis. *Apoptosis* (programmed cell death) describes a set of regulated physiologic and morphologic changes leading to cellular death. This is the principal mechanism by which embryogenesis occurs or senescent /dysfunctional cells are normally eliminated. In addition, cell death via apoptosis is the dominant process leading to the termination of inflammation once infection has subsided. However, proinflammatory cytokines may delay apoptosis in activated macrophages and neutrophils. This effect may prolong or

augment the inflammatory response, thereby contributing to the development of multiple organ failure. Derangements of apoptotic cell death are also believed to play a critical role in the tissue injury of sepsis. (33) Apoptosis is normally a physiologic mechanism to selectively limit cell populations with rapid proliferation (e.g., gut epithelium). When exposed to various inflammatory mediators, such as endotoxin, cytokines, and reactive oxygen species, parenchymal and endothelial cells respond by the induction of one of two programs of stress gene expression. When subsequently exposed to endotoxin, these cells undergo accelerated apoptosis. Gut epithelial apoptosis is an important factor in an animal model of Pseudomonas sepsis (34).

iv) Tropical Infections: As per data from developing countries, tropical infections like scrub typhus, malaria, dengue, leptospirosis and enteric fever were associated with AKI. A study of all patients with tropical infections done in this centre showed an incidence of 41.1% of AKI; of which, 17.4%, 9.3% and 14.4% were in the Risk, Injury and Failure classes, respectively (35). The pathophysiology in leptospirosis leading to AKI is postulated to be due to a vasculitis that is commonly seen in the disease. In the kidney, leptospires migrate to the interstitium, renal tubules, and tubular lumen, causing interstitial nephritis and tubular necrosis. Hypovolemia due to dehydration or altered capillary permeability may also contribute to the development of renal failure (36).

Scrub typhus also known to cause AKI has a pathophysiology which leads to occlusive thrombosis and ischemic necrosis. However, these are not the fundamental pathologic basis for tissue and organ injury. Instead, increased vascular permeability, with resulting edema, hypovolemia, and ischemia, is responsible. Hypovolemia leads to prerenal azotemia and (in 17% of cases) hypotension. Renal failure, often reversible with rehydration, is caused by acute tubular necrosis in severe cases with shock (37).

AKI is common among adults with severe falciparum malaria. The pathogenesis of renal failure is unclear but may be related to erythrocyte sequestration interfering with renal

microcirculatory flow and metabolism. Clinically and pathologically, this syndrome manifests as acute tubular necrosis, although renal cortical necrosis never develops. Acute renal failure may occur simultaneously with other vital-organ dysfunction (in which case the mortality risk is high) or may progress as other disease manifestations resolve. In survivors, urine flow resumes in a median of 4 days, and serum creatinine levels return to normal in a mean of 17 days. Early dialysis or hemofiltration considerably enhances the likelihood of a patient's survival, particularly in acute hypercatabolic renal failure (38) .

v) Intra abdominal hypertension (IAH): A new concept in the etiology of AKI in the ICU is intra abdominal hypertension. In healthy individuals, a normal pressure (IAP) is less than 5 to 7 mm Hg (39) according to the World Society of Abdominal Compartment Syndrome (ACS), and is usually diagnosed by measuring a patient's intravesical pressure. An upper limit of 12 cms is generally accepted by the Society (39).Abdominal Perfusion Pressure = Mean Arterial Pressure (MAP) - Intra abdominal pressure (IAP)

Normal = 60 mm of Hg (39).

A sustained IAP (intra abdominal pressure) of > 20 mm Hg and abdominal perfusion pressure of <60 mm Hg occurring in association with a new and attributable organ dysfunction or failure defines the syndrome (40). Primary ACS occurs in the setting of injury and stems from the hemorrhage and edema. Secondary ACS occurs in both surgical and medical patients after excessive resuscitation due to fluid therapy leading to ascites and visceral edema. This raised ACS can lead to poor perfusion to the kidneys. Therapeutic interventions include surgical decompression and other local therapies like- prosthetic grafts, skin grafts or flaps for abdominal wall reconstruction. However, no RCTs have been done to show the benefit of one therapy over the other. Thus, currently the gold standard of therapy for ACS is surgical decompression.

vi) Hepatic dysfunction: An increasing number of patients with severe liver dysfunction are admitted to the ICU for stabilization and organ-specific support, including liver transplantation. Global impairment of hepatic performance frequently results in pathologic organ interactions that limit the potential for recovery. One of the most notable of these interactions is the hepatorenal syndrome. This is a fatal complication of end- stage liver disease characterized by the progressive development of oliguria and low urine sodium excretion. The syndrome can occur in the setting of either acute or chronic liver disease, and portal hypertension is important in the pathogenesis. The patient with the hepatorenal syndrome also has a number of systemic circulatory abnormalities induced by liver disease and/or portal hypertension, but the exact pathologic role of these abnormalities in the development of oliguria is uncertain.

The following mechanisms are implicated in the development of hepatorenal syndrome (HRS):

1. Splanchnic and peripheral vasodilatation with reduction in effective arterial volume causes activation of mechanisms leading to intense renal vasoconstriction and functional AKI. HRS is a diagnosis of exclusion and all other causes of AKI (especially prerenal azotemia) have to be considered and excluded (41).

2. Circulatory dysfunction in cirrhotic patients may cause HRS. It contributes to the high incidence of renal failure in cirrhotic ICU patients. Fluid therapy may aggravate renal failure by increasing ascites and intra abdominal pressure. Information regarding this condition is still incomplete (41). It is reasonably well established that diminished systemic blood pressure is not the primary cause of renal insufficiency. Rather, intrarenal preglomerular vasoconstriction mediated by unknown stimuli is the major defect in the hepatorenal syndrome, manifested by relative ischemia. Current data point to abdominal renal sympathetic innervation as one of the more likely major causes of this vasoconstriction.

After exclusion of systemic intravascular volume depletion and other causes of oliguria, dialysis therapy is indicated when liver transplantation or recovery of liver function is anticipated; terminal supportive care is appropriate when these outcomes are not options.

vii) Toxin and drug induced renal injury: Drugs with direct nephrotoxic effects may induce renal injury by several mechanisms. Most commonly, renally excreted drugs can exert direct toxic effects on renal tubules inducing direct cellular injury and death in *acute tubular necrosis* or induce *inflammation* in the renal interstitium in acute interstitial nephritis. These are generally caused by aminoglycosides.

Other types of nephrotoxic tubular injury include *osmotic nephrosis* induced by hypertonic solutions and *tubular obstruction* by drug precipitation (e.g. crystalline nephropathy caused by acyclovir and indinavir). Nephrotoxic acute tubular necrosis is generally a dose dependent phenomenon that predictably occurs in patients at high risk for renal injury (older patients, pre existing renal disease, multiple nephrotoxic agents used) and is characteristically noninflammatory in nature. In contrast, acute (allergic) nephritis is an idiosyncratic inflammatory response to drug exposure. Agents commonly implicated in these are penicillins; non steroidal anti inflammatory drugs (NSAIDs) and calcineurin inhibitors. Drugs also may be indirectly nephrotoxic by *modulating intra renal blood flow*, thus rendering the kidneys vulnerable to ischemia and injury in the case of decreased renal blood flow such as those seen in angiotensin converting enzyme inhibitors (ACEIs), and NSAIDs. Therapeutic agents have been associated with the development of glomerular disease or *vasculitis*; however, these are relatively rare complications of medical therapy commonly seen with penicillamine, gold and hydralazine (42).

Radiocontrast has been attributed to an increase in the risk of developing AKI. This is because in a patient who is already critically ill with severe metabolic illness like sepsis with superimposed renal vasoconstriction, impaired vasodilatation, and medullary hypoxia, it can lead to an oxidative

stress and direct tubular injury. Iodinated contrast being water soluble dwells in the urinary space of the glomerulus and renal tubules, causing direct toxicity to the renal tubular cells (24).

RENAL PROTECTION STRATEGIES:

There have been many renal protection strategies suggested for the prevention of AKI. They are

1) Hydration and volume loading.

2) Maintaining renal perfusion pressure.

3) Avoiding nephrotoxic medications like, amphotericin B, amino glycosides and prevention of radio contrast nephropathy.

4) Pharmacologic protection.

In the prevention of AKI (at least in some causes), the composition of fluid and the optimal rate of infusion has yet to be defined. Renal perfusion therapy is helpful in reducing the AKI incidence, but there is no definite quantitative data to guide in the therapy for the same. However, it seems one of the best ways to prevent AKI. The therapy for maintaining adequate renal perfusion pressure has to be individualized for each patient.

Pharmacologic protection:

There have also been pharmacologic therapies suggested for AKI prevention. Not all have been deemed beneficial. These therapies are:

a) **Loop diuretics**: Meta analyses have shown no role for loop diuretics in the prevention of AKI (43).

b) **Dopamine agonists**: Dopamine agonists and dopamine have been found to have no benefit in reducing incidence of renal injury (44). However, fenoldopam a selective dopamine-1-receptor agonist, has been shown to increase renal blood flow and glomerular filtration rate. A recent single centre study as well as meta analysis showed that fenoldopam reduced the incidence of renal injury in patients in ICU patients or those undergoing major surgery. It does not seem to show benefit in contrast induced nephropathy (45).

c) Natriuretic peptides: Natriuretic peptides like aniritide have been tried, but there is still no conclusive evidence as to its use in AKI, and as of now is not recommended (46).

d) Calcium channel antagonists: A meta analyses of RCTs done in post transplant patients with a calcium channel blocker called isradipine was found to show no benefit, even though the trials included were heterogeneous and used varying doses of the drug (47).

e) N-Acetyl Cysteine: N- acetyl cysteine (NAC) has antioxidant and vasodilatory properties. Although not well understood, a possible mechanism of benefit in contrast-induced nephropathy involves minimizing both vasoconstriction and oxygen free radical generation after radiocontrast agent administration. N-Acetyl cysteine has been found to be beneficial in contrast induced nephropathy as shown in meta analyses which evaluated its use and found that it prevented the serum creatinine from rising. But, the benefit was found to

be found only in prevention of serum creatinine from rising. There was no improvement in glomerular filtration rate. However, current recommendations are that NAC should be used prior to contrast being given(48).

MANAGEMENT OF ESTABLISHED AKI:

The modality of treatment in AKI used is either continuous renal replacement therapy (CRRT), intermittent hemodialysis(IHD)or slow extended daily dialysis (SLEDD) Randomized controlled trials have not shown a benefit of CRRT in mortality over IHD (49).

Currently there is no consensus on specific dosing for dialysis nor the right time for dialysis can be made in patients. The two principal outcomes that have been examined with CRRT and IHD are patient survival and recovery of renal function. A paucity of evidence exists that have examined these issues. However, current data suggest that survival and recovery of renal function are similar with both CRRT and IHD. The majority of studies comparing CRRT and IHD have been observational or retrospective case series (50,51,52,53,54). There appears to be no survival benefit associated with CRRT after adjustment for severity of illness (55,56).

A paucity of data exists concerning the effect on mortality of peritoneal dialysis (PD) versus intermittent hemodialysis (IHD) or continuous renal replacement therapies other than PD in patients with acute renal failure. Most studies had shown that the mortality and incidence of renal recovery with acute PD was at least comparable to hemodialysis (57) To address this question, a prospective study was performed in Vietnam in which 70 patients with acute renal failure due to either malaria or sepsis (48 and 22 individuals, respectively) were randomly assigned to either peritoneal dialysis or continuous venovenous hemofiltration (CVVH) (58). A markedly increased risk of death was observed among the group administered PD (47 versus 15 percent, odds ratio 5.1, 95 percent CI 1.6 to 16). In addition, the mortality rate for patients on CVVH was unusually

low. Possible reasons for the poorer survival in the PD group include lower overall creatinine clearance; use of acetate (not bicarbonate) in the PD dialysate, use of rigid PD catheters and other PD-specific factors that are not yet defined (59).

In summary, there are a few factors that can be modified and can lead to a reduction in the number of patients with AKI and also in associated morbidity and mortality (18),(22).

Although there have been studies on renal failure in ICU patients, most of these are for Western centers. In India, patients are admitted to ICUs are younger, more likely to have a reversible cause such as infections (scrub typhus, leptospirosis, dengue fever, malaria) poisoning or envenomation and have lesser co morbidities. The resources available to treat AKI are also limited in most Indian settings. In view of this, the above study was done to stratify the data into the prevalence, risk factors and outcomes of AKI in our setting.

AIMS OF THE STUDY

To study Acute Kidney Injury (AKI) in a tertiary care Medical Intensive Care Unit in order to document the incidence, evaluate the risk factors for its development and study the outcomes in an Indian setting.

PATIENTS AND METHODS

Inclusion Criteria

All critically ill patients admitted in Medical Intensive Care Unit of the hospital.

Exclusion criteria

Nil.

Sample size

Since most of the data is from Western ICUs and as the patient profile is different from those in India, these numbers could not be used. The incidence of dialyzed patients in the Medical ICU was used to calculate the sample size, as that number would give an estimate of incidence with definite failure (F according to the RIFLE criteria) getting admitted. An estimate of the number of patients with the F class of AKI were identified in the patients admitted in ICU using the dialysis database. The number was 33 out of a total of 132 patients admitted to ICU (25%).

Thus substituting p as 25% and q as 75% using the formula

$$\sqrt{p \times q} / n$$

Where p was sample proportion (25), q was (100-p= 75) and n was 132. A standard error of 3.87 was obtained. A precision of 8% was obtained from this value with a Z of 1.96 being set and with a confidence interval of 95% to estimate an alpha error of 0.05 using the formula

$$n = z^2 \times p \times q / \text{precision}^2$$

where z=1.96, P=25, Q =75, and precision was 8%,a sample size of 113 was obtained.

It was also intended to study 10 variables likely to be risk factors (age, gender, hypotension, primary diagnosis, co morbidities, APACHE II and MODS scoring systems, liver diseases, nephrotoxic drugs, radiocontrast exposure, duration of mechanical ventilation.) and using the rule of thumb of 10 patients for each risk factor, a figure of 100 was obtained which was about the same as obtained by the above formula.

Data Collection

a) Baseline Patient Information

At the initial admission baseline profile demographic data profile (age, gender, and basic diagnosis including reason for admission including other co morbidities) were collected as per the enclosed proforma (Appendix 1). Their baseline clinical metabolic, hematological parameters were followed up during ICU stay as per protocol. Data collection also included complications, investigations and dialysis details.

b) Follow up assessment in ICU

ICU readings were recorded every hour vitals viz: blood pressure, pulse rate, respiratory rate, sensorium, inotropic supports, ventilatory supports. The highest and lowest readings over the whole day were collected in the data sheet. Details of complications, daily arterial blood gas monitoring (ABG) parameters, metabolic and hematological parameters with information about antibiotics, and change in drug orders and use of radio contrast agents were also included. Relevant information about the desired factors of interest was gathered which included: a) co morbidities, b) duration of mechanical ventilation, c) hepatic dysfunction, d) APACHE II scoring and MODS scoring, e) hypotension, f) nephrotoxic drugs and g) exposure to radiocontrast. A univariate analysis on each of them to assess significance was done, followed by a multivariate analysis on those factors found to be significant in the initial univariate analysis.

Statistical Methods

Data entry was undertaken by a single investigator using Microsoft Excel. Data analysis was done using Statistical Package for Social Sciences Version 17. The degree of correlation between the onset of AKI with 10 factors under study and also the progression to death were studied and a univariate and multivariate analysis was performed. The method involved cross tabulation followed by logistic regression and Chi square analysis.

RESULTS

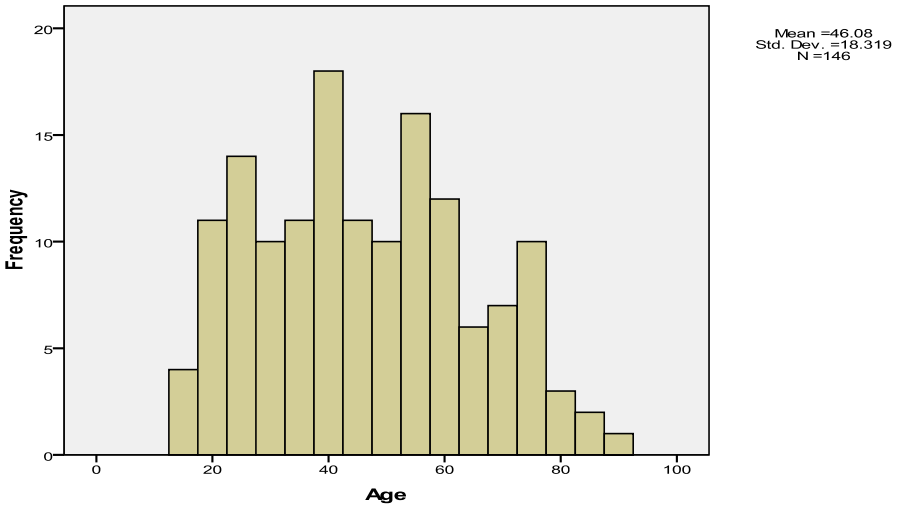
1. Patient profile

A total of 146 patients were included in the study from September 2009 to January 2010. The total number of patients admitted to the Medical ICU during the same period was 146 out of which 114 patients developed AKI which gave an overall incidence of AKI at 78.1%.

Parameter	Value
Total number of patients	146
Mean (SD) age in years	46.08 (±18.319)
Age range in years	15-90
Male: Female ratio	1.05:1

a) Age distribution The ages of patients ranged from 15 years to 90 years old. The mean (± SD) age was 46.08 years (± 18 years).

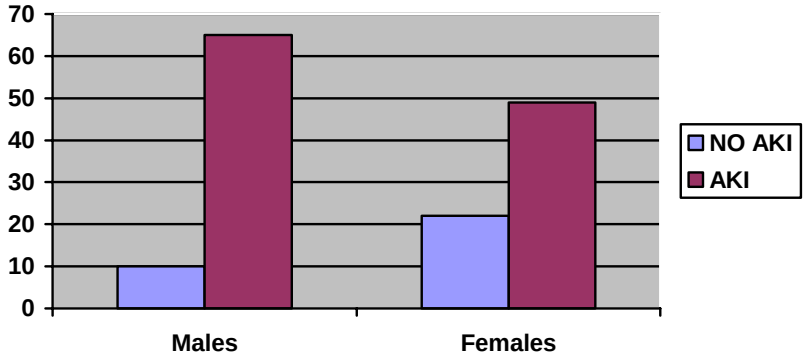
	30 years	30-45 years	46-60 years	60 years	Total
NO AKI	13 (35.14%)	7 (17.5%)	3 (9.38%)	9 (24.32%)	32
AKI	24 (64.86%)	33 (82.5%)	29 (90.62%)	28 (75.68%)	114
Total	**37**	**40**	**32**	**37**	**146**



The distribution of patients across various age groups was plotted and accordingly they were divided into 4 groups and the incidence of AKI in each age subgroup was analyzed to look for association with AKI. It was found on analysis that as the age advanced the incidence of AKI increased and it was found to be statistically significant with a p value of 0.04.

b) Gender: There were a total of 146 patients out of which 71 were females and 75 were male. Out of these 49 women and 65 males developed AKI. The p value for the same was 0.008 implying that this difference was significant.

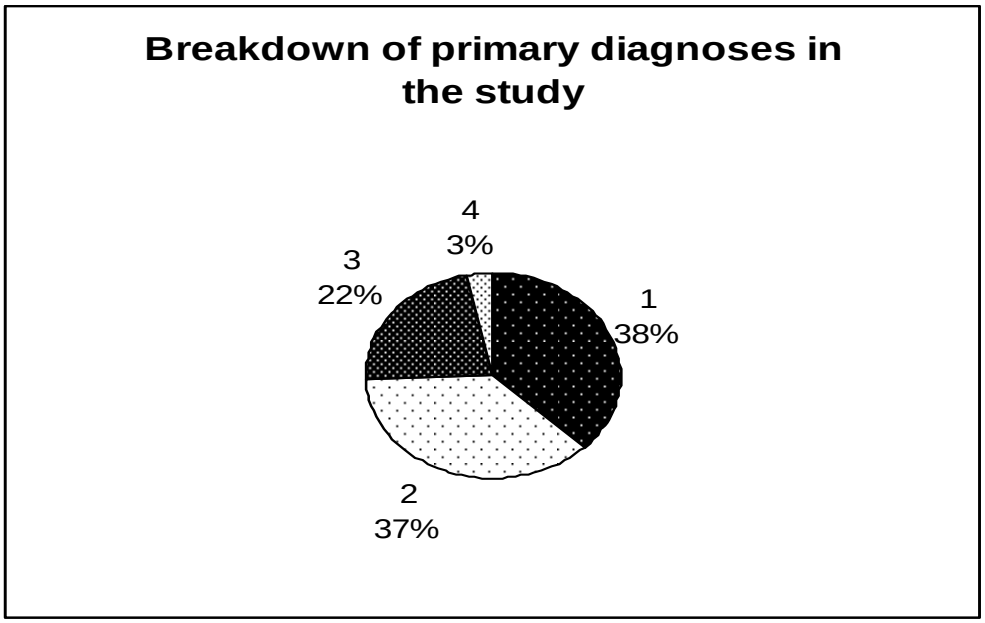
	Males	**Females**	**Total**
No AKI	10	22	32
AKI	65	49	114
Total	**75**	**71**	**146**



2. Primary Diagnoses:

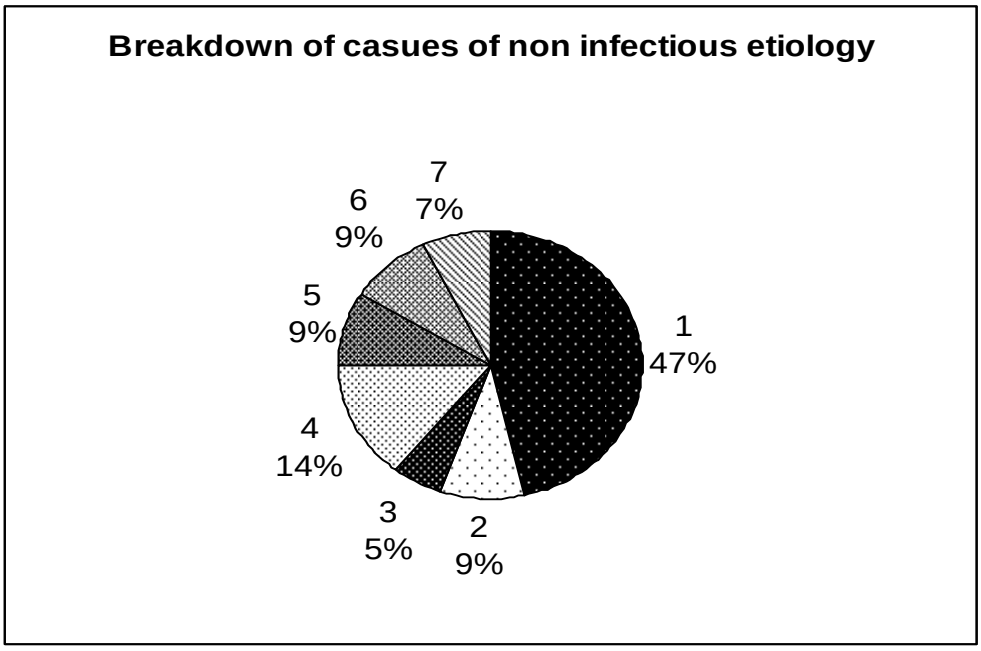
Primary Diagnoses	Number (percentage)
Non infectious	56 (38.4%)
Non tropical bacterial infections	53 (36.3%)
Tropical infections	32 (21.9%)
Liver dysfunction	5 (3.2%)

1- Non infectious diseases, 2- Non tropical infectious diseases, 3- Tropical infections, 4- Liver diseases



a) **Non infectious causes**: This included acute cardiac failure with pulmonary edema, non infectious causes of SIRS like (acute pancreatitis, pregnancy related illnesses etc), envenomations, suicidal hangings and cerebrovascular accidents

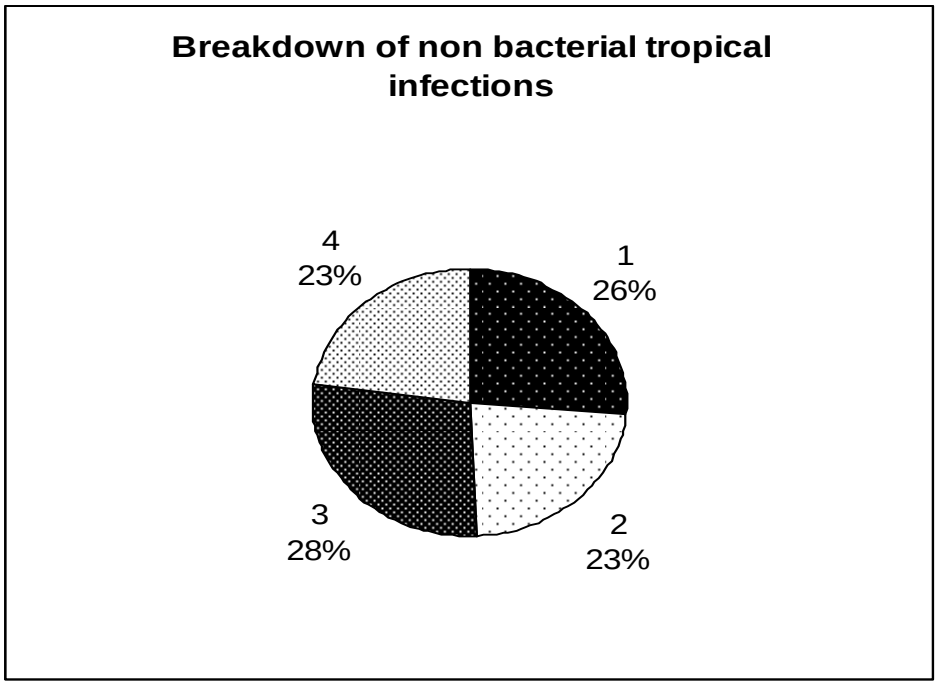
Diagnostic category	**Number (percentages)**
Cardiac pathology	26 (46.4%)
Pregnancy related illnesses	5 (8.9%)
Dyselectrolytemia	3 (5.3%)
Cerebrovascular accidents (CVA)	8 (14.2%)
Poisonings	5 (8.9%)
Acute pancreatitis	5 (8.9%)
Envenomations which included snakebites as	4 (7.3%) out of which 3 were snake bites.



1- Cardiac pathology 2- Pregnancy related illnesses, 3- Dyselectrolytemia, 4- CVA, 5- Poisonings, 6- Acute pancreatitis, 7- Envenomations

b) **<u>Non tropical bacterial infections</u>**: These included all infections caused by agents which were not confined to the tropics. The most common were sepsis and septic shock caused due to gram negative or gram positive bacteria. Viral encephlitides, fungal and parasitic infections and infections in post transplant patients were also included. The analysis was based on the etiological agents identified i.e. if it was an agent not confined to the tropic then it was included in this category.

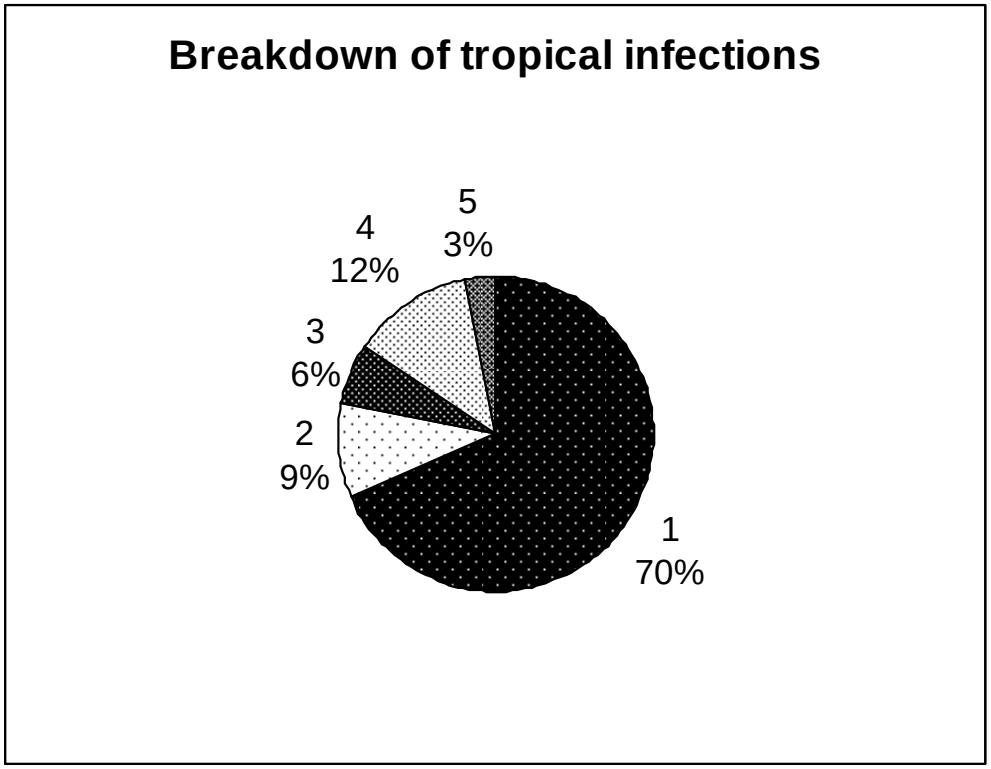
Etiological agent / Syndrome	**Number (percentages %)**
Gram negative bacteria	14 (26.41%)
Gram positive bacteria	12 (22.64%)
Viruses	15 (28.30%)
Unknown agent but with a definite focus	12 (22.64%)



1- Gram negative bacteria, 2- Gram positive bacteria, 3-Viruses, 4- Unknown agent with a definite focus

c) **Tropical Infections**: These were studied separately as they were postulated to be one of the risk factors for development of AKI in the ICU. These included patients with malaria, dengue, scrub typhus, leptospirosis and tuberculosis.

Tropical infections	**Number (percentages %)**
Scrub typhus	22 (68.75%)
Dengue fever	3(9.375%)
Tuberculosis	2(6.25%)
Malaria	4(12.5%)
Leptospirosis	1(3.125%)



1- Scrub typhus, 2- Dengue fever, 3- Tuberculosis, 4- Malaria, 5- Leptospirosis

d) **Liver diseases:** There was also a separate diagnostic category of patients admitted with liver disorders. This included those with acute liver diseases and those with acute on chronic liver diseases. The duration for differentiating acute and chronic liver disease was taken as 6 months. (42) This was included to study the correlation between liver diseases and AKI.

Diagnosis	**Number (percentages %)**
Acute fatty liver of pregnancy	1 (20%)
HELLP syndrome (hepatitis, ,elevated liver enzymes, low platelets)	1 (20%)
Budd Chiari syndrome	1 (20%)
Decompensated chronic liver disease	2 (40%)

Primary Diagnosis and AKI

This table shows the breakdown of patients into those who had AKI and those who did not have AKI.

	Non infectious	**Non Bact. Trop Infec.**	**Tropical Infections**	**Liver diseases**	**Total**
No AKI	18	6	8	0	32
AKI	38	47	24	5	114
Total	56	53	32	5	146

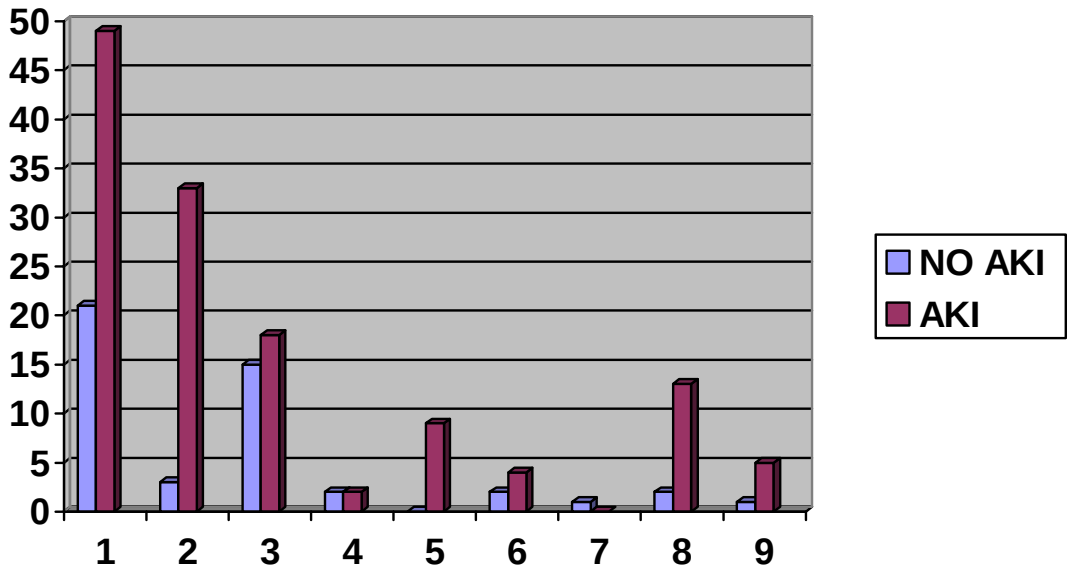
The P value was 0.037 for those with non tropical bacterial infections, 0.56 for tropical infections and 0.78 for non infectious diseases.

3. Co morbidities of patients admitted in ICU:

Co morbidities in patients were studied for an association with AKI. This was the profile of all patients admitted to ICU

Co morbidities	Number (Percentage)
None	70 (47.9%)
Diabetes Mellitus	47 (32.1%)
Hypertension	32 (21.9%)
Chronic Kidney Disease (CKD)	9 (6.2%)
Chronic Liver Disease (CLD)	6 (4.2%)
Malignancies	15 (10.3%)
Connective tissue disorders	1 (0.7%)

The break up according to AKI in each category was as follows:



1- Nil, 2 – Diabetes, 3- Hypertension, 4- Ischemic heart disease, 5- Chronic kidney disease, 6- Chronic Liver disease, 7- Connective tissue disease, 8- Malignancies, 9- Miscellaneous

The Chi square analysis revealed a p value of 0.38 implying that secondary diagnosis was not significant as risk factor for AKI, however on evaluation of each individual disease, diabetes was found to be a risk factor for AKI.

4. APACHE II and MODS scores*:*

APACHE II score among patients with AKI and those without AKI was done by calculating mean scores in both groups and then performing tests of significance. The mean score in patients with AKI was and those without AKI was as mentioned in the table below.

	Mean APACHE 2 score	**Std.deviation**	**Std. error**
NO AKI	22.06	7.62	1.35
AKI	27.93	9.07	0.85

The p value was 0.001 showing a significant association between a high APACHE II score and AKI.

A similar method was used for assessing relation between MODS scores and AKI, wherein mean scores in both AKI and non AKI groups were calculated and then a paired t- test was done to see if this difference was significant.

The mean MODS score in AKI and in those with no AKI was as shown in the table below:

	Mean MODS score	**Std. Deviation**	**Std. Error**
NO AKI	7.88	2.84	0.5
AKI	8.8	2.94	0.27

The p value was .112 suggesting no statistically significant relation between AKI development and MODS score.

5. **Risk factors**

i) Hypotension:

Hypotension was defined as Mean arterial pressure (MAP) of less than 70 mm Hg (10-11) where

MAP = Diastolic pressure + 1/3 rd of pulse pressure

Pulse pressure being the difference between the systolic and diastolic blood pressure [42].

The MAP was available on all ICU patients on monitors.

Hypotension as one of the causes of AKI in these patients was also analysed

.	**Hypotension absent**	**Hypotension present**	**Total**
No AKI	23	8	31
AKI	47	50	97
Total	70	58	128

The p value was 0.010 for developing AKI suggestive of significant association between AKI and hypotension.

ii) Duration of ventilation

	Number of patients	**Mean**	**Std.**	**Std. Error**
NO AKI	32	6.9	0.47	0.78
AKI	99	7.7	0.44	0.12

There was no correlation between duration of ventilation and AKI. Means for duration in the two groups (with and without AKI) were calculated and then analysed for significance. The P value was 0.275 showing no association between the two risk factors

iii) Liver dysfunction:

In those with hepatic dysfunction, bilirubin levels, transaminase levels (cut off of 40 IU/L) and albumin levels (level less than 3.5 mg/dl) were used separately to assess if each of this had any bearing on the risk of developing AKI. The difference in these patients and those who were included with liver diseases in the primary diagnosis was as follows. These patients had liver involvement in the form of transaminitis and mild hyperbilirubinemia, but there was no evidence of hepatic failure as demonstrated by ammonia levels, prolonged prothrombin time and hepatic encephalopathy.

a) Bilirubin levels:

Patients were classified according to bilirubin values into those who developed AKI and those who did not and then performed tests of significance to see if there was a statistically difference in the two groups.

	Normal Values	**Abnormal Values**	**Data not available**	**Total**
NO AKI	21	4	7	32
AKI	65	37	12	114

The P value for correlation of hyperbilirubinemia with AKI was 0.132 showing no correlation between the two.

b) **Enzyme levels:**

A similar method to the one used for assessing relationship between AKI and bilirubin was used for assessing relationship between the enzymes and AKI. The enzymes studied were SGOT and SGPT. The lab cutoffs for both of them were 40 IU/dl. The enzymes were studied separately for their relationship to AKI.

SGOT and AKI evaluation

	Normal Values	**Abnormal Values**	**Data not available**	**Total**
NO AKI	12	13	7	32
AKI	32	70	12	114
Total	44	83	19	146

SGPT and AKI evaluation

	Normal Values	**Abnormal Values**	**Data not available**	**Total**
NO AKI	16	9	7	32
AKI	55	44	12	114
Total	71	53	19	146

The P values for correlation between SGOT and SGPT with AKI respectively were 0.143 and 0.503 suggesting no significant association between AKI and transaminase levels.

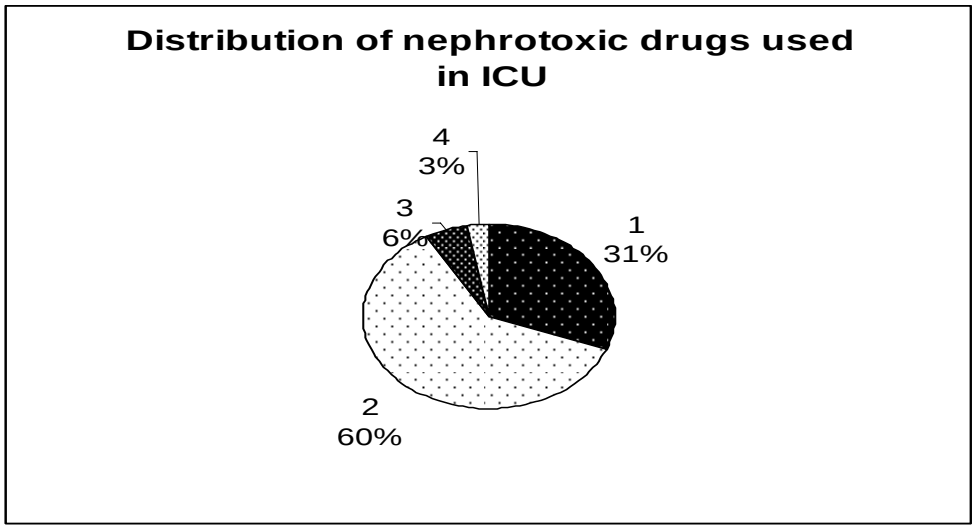
c) Serum Protein and serum albumin levels: As part of evaluation between AKI and liver abnormalities, a test of statistical significance was done between abnormal albumin levels and those who developed AKI.

	Normal Albumin	Low Albumin	Data not available	Total
NO AKI	16	9	7	32
AKI	38	62	12	114
Total	54	71	19	146

The correlation between AKI and hypoalbuminemia was found to be significant at 0.027 suggesting a positive association.

iv) Potentially Nephrotoxic drugs:

Class of drugs	Number (percentages)
None	45 (30.8%)
Antibiotics	89 (61%)
Cardiac drugs (ACEIs, digoxin)	8 (5.5%)
Miscellaneous (Phenytoin etc)	4 (2.7%)



1- None, 2- Antibiotics, 3- Cardiac drugs, 4- Miscellaneous

The association between AKI and potentially nephrotoxic drugs was as follows:

	No exposure to nephrotoxic drugs	**Exposed to nephrotoxic drugs**	**Total**
NO AKI	10	22	32
AKI	35	79	114
Total	**45**	**101**	**146**

The drugs most commonly used in the ICUs were antibiotics (beta lactams, were most common), cardiac drugs like ACEIs, digoxin and diuretics, and others like acyclovir phenytoin , heparin, ranitidine, omeprazole, and digoxin.

The P value for association between AKI and nephrotoxic drugs was 0.556 implying no statistical significance.

v) Radio contrast exposure :

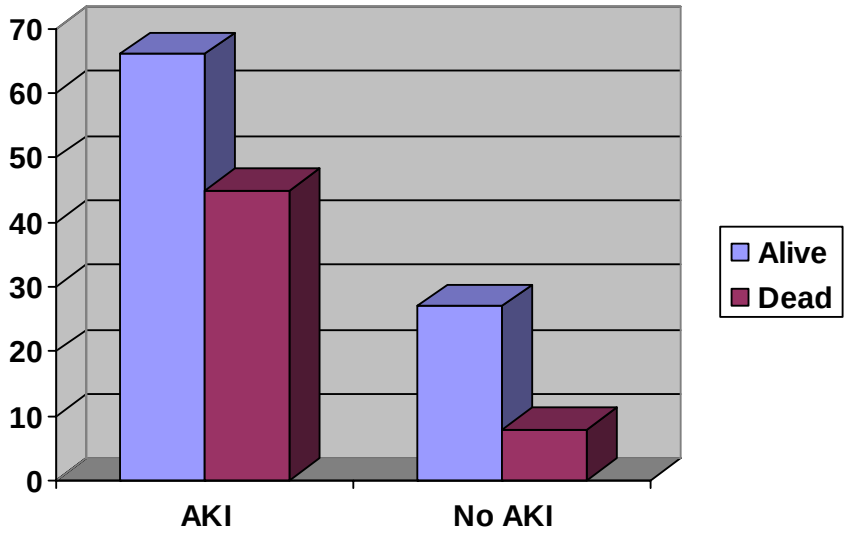
Exposure to radiocontrast was one of the risk factors postulated to predispose to AKI. This too was studied for relation to AKI in the ICU.

	Not Exposed to	**Exposed to**	**Total**
NO AKI	25	7	32
AKI	105	9	114
Total	130	16	146

The P value in this was 0.03 implying significant association between developing AKI and exposure to radiocontrast.

6. Outcomes*:* The association between AKI and mortality was evaluated to assess the effect of development of AKI on mortality.

.	**Alive**	**Dead**	**Total**
NO AKI	27 (77.1%)	8 (22.9%)	35
AKI	66 (59.5%)	45 (40.5%)	111
Total	93	53	146

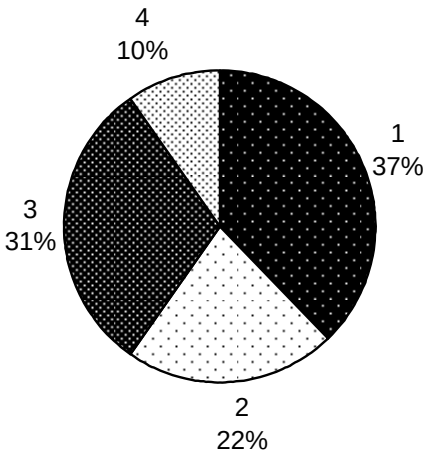


The significance of this was 0.043 showing a significant association between AKI and death.

A breakdown according to AKI class was done to assess the incidence of each class and the severity of AKI in this ICU. The results were as below. As patients were not followed out of ICU, there were no patients in the L category (Loss according to RIFLE criteria) who were identified.

Class of AKI	Incidence (percentage)
R (Risk)	43 (37.7%)
I (Injury)	25 (21.92%)
F (Failure)	35 (30.7%)
L (Loss)	0
E (End stage renal disease, ESRD)	11 (9.64%)

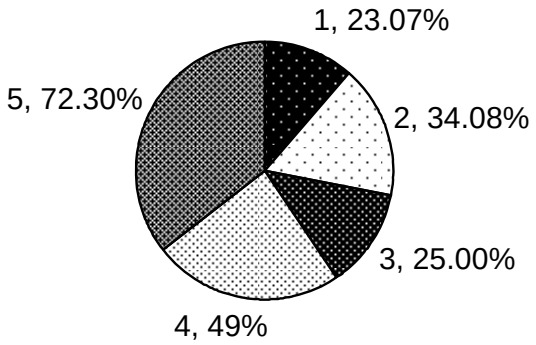
Breakdown according to AKI Class



1- R (Risk), 2- I (Injury), 3- F (Failure), 4- E (ESRD)

A subgroup analysis was performed to look for correlation between class of AKI and survival outcomes.

AKI Class	Alive	Dead	Total
NO AKI	26	6 (23.07%)	32
Risk	28	15 (34.8%)	43
Injury	18	7 (25%)	25
Failure	18	17 (48.6%)	35
Loss	0	0	0
ESRD	3	8 (72.3%)	11
Total	93	53	146

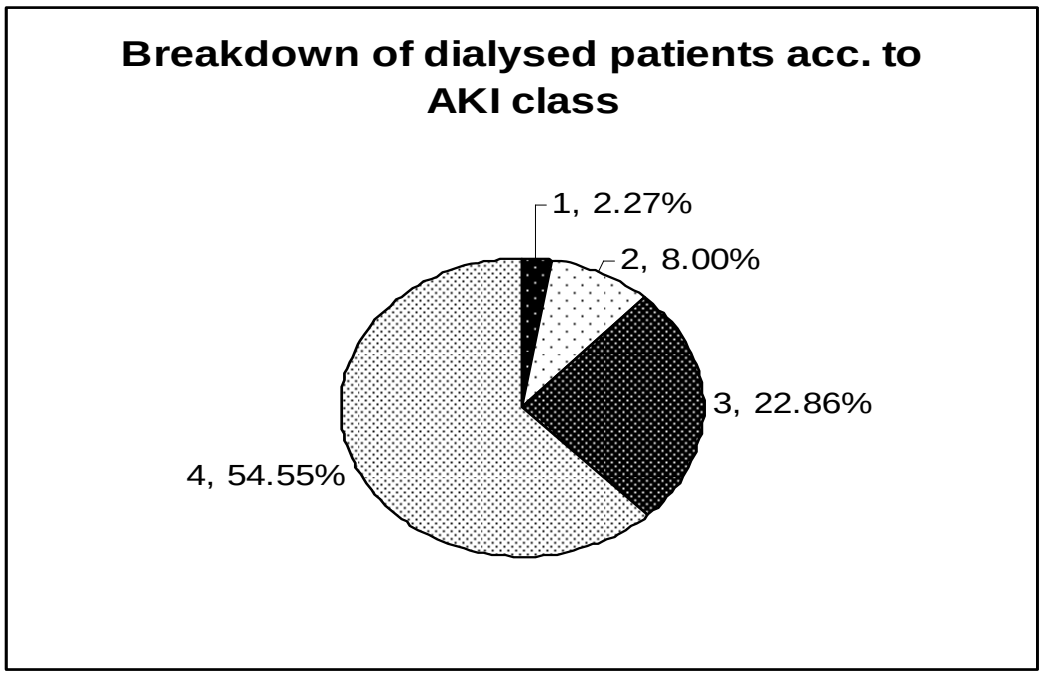


1-No AKI, 2- Risk, 3- Injury, 4- Failure, 5- End stage renal disease

The p value noted for this was 0.011 implying that the class of AKI had a bearing on survival outcomes. As per the table above, severity of class coincided with poor survival outcomes.

7. Treatments

	NO AKI	Risk	Injury	Failure	ESRD	Total
No HD	30	42	23	27	5	129
Received HD	0	1	2	8	6	17
Total	30	43	25	35	11	146
Percentage	0	2.27%	8.00%	22.86%	54.55%	11.64%



1- Risk, 2- Injury, 3- Failure, 4- ESRD

Patients at the more severe end of the spectrum of AKI received HD and a more severe classification of AKI was associated with a poorer survival outcome. The number of patients in the L category could not be ascertained as the patients were not followed out of ICU.

MULTIVARIATE ANALYSIS:

A muitvariate analysis was done at the end of the univariate analysis taking into consideration all the factors that were found to be significant and the results were as follows:

Variable	P Value
Age	0.03
Gender	0.02
Diabetes	0.01
Hypotension	0.01
APACHE II score	0.02
Non tropical bacterial infection	0.02
Radiocontrast	0.16
Hypoalbuminemia	0.01

From this multivariate analysis we concluded that age, gender, diabetes , hypotension, a high baseline APACHE score, non tropical bacterial sepsis and hypoalbuminemia were predictors of developing AKI as they had a statistically significant association with AKI. The only factor found to be significant in the univariate but not significant in the multivariate analysis was radiocontrast nephropathy.

DISCUSSION

Acute Kidney Injury has been widely reported in ICUs and has been associated with multiple etiologies and risk factors- some of which are reversible (viz: hypotension) and others which are irreversible (viz: liver failure).

This study was conducted as there was inadequate published data in a tropical ICU setting. One study carried out in an ICU in a tertiary care teaching hospital in India, found a positive association between age, sepsis, APACHE score and MODS in the development of AKI (22).

The unique case burden seen here is unlike those in Western ICUs, where in ICU patients a) age is higher b) multiple co morbidities are present and patient profile may include high number of complicated post op cases (21,23,25,26) and mortality could be higher due to these factors. This is unlike an ICU population in India where the age is younger, co morbidities are less, and infections like malaria, scrub typhus and leptospirosis may form the bulk of patients. Thus, this study was done to see how the people who developed AKI in this ICU setting were different as compared to the data available from Western ICUs. It was also to observe the commonest AKI class in the ICU and its effect on mortality.

Hoste et al (13) found that in the ICU setting in Western centers, there were a higher percentage of patients with R as compared to I and F. There were no patients with L and E class of AKI. The results seen there were as follows: patients with maximum RIFLE class R, class I and class F had hospital mortality rates of 8.8%, 11.4% and 26.3%, respectively, compared with 5.5% for patients without acute kidney injury. As mentioned in the literature review in the beginning, the RIFLE classification has been validated externally and has been found to be a better predictor of AKI than serum creatinine alone.

A. Patient profile:

i) Overall Incidence:

The overall incidence was 78.1% which was more than that reported in other studies (1),(21), which could be because of the hospital being a tertiary care referral centre and the lag time for presentation for patients form various hospitals.

ii)Age:

This study found that an older age was a risk factor for developing AKI. This has been corroborated with other studies in both Indian and Western cohorts (18,22,29). The reason age is linked to AKI could be due to a reduced physiological reserve or increasing co morbidities with increasing age

iii)Gender:

Gender was found to be a significant factor in development of AKI in this study. This is a finding that had been reported in a earlier studies while studies were being conducted to evaluate the nephrotoxicity of other factors (32,33). However, now the male gender is recognized as a well known factor for developing AKI (34,60).

B. Primary diagnosis:

As part of the analysis, primary diagnoses (the main reason for admission into ICU) were classified into non infectious, non tropical bacterial infections, tropical infections and primary liver disorders. The reason is because one of the common conditions causing renal failure in this setting are tropical infections. It was found that patients with bacterial infection and associated sepsis had higher risk of development of AKI. There was no higher risk for development of AKI found in patients with tropical infections in this study. The role of sepsis in causing AKI though not fully well defined has been well documented and this was confirmed by this study (61). Envenomations esp. snake bites were not considered for analysis as there were only 3 patients in total and were too small a number to study for any associations. Tropical infections have been well documented to have AKI (35). However, this study did not find it as association as a risk factor for developing AKI. The reason could be that in the case of scrub typhus, empirical Doxycyline is started early during the course of admission for any patient with high clinical suspicion (eschar, hepatitis, renal failure and thrombocytopenia). This disease is well known for its rapid response to antibiotics, which can explain why patients who came to ICU received early antibiotics and thus may not have developed AKI. There was only one case of leptospirosis during the course of the study and hence, this study is underpowered to study any association between the two. Dengue is a rapidly reversible cause of AKI if isotonic fluids are given to the patient once shock develops, as was the case in most patients coming to ICU. Malaria is a very common disease here and most patients who are admitted have already received artesunate or quinine prior to presentation, thus again leading to less patients presenting with severe renal dysfunction.

A univariate analysis was done on the various factors that were involved in the liver function tests done in this hospital viz: bilirubin levels, albumin levels and transaminases. Hence, various components of liver function tests were used to ascertain if any of them had any association with AKI. The patients who came with acute liver failure (hepatic disease) were only 5 in number hence, this study was underpowered to study any relation between the two, though all patients who were admitted with this condition, were found to have AKI. The rest of the analysis was in patients with mild liver dysfunction which was probably a secondary manifestation of a MOSF. In these only a low albumin level (below 3.5 mg/dl) showed a significant co relation with AKI in the multivariate analysis. The correlation between AKI and hypoalbuminemia can be explained by a) albumin's role as a negative phase reactant, the sicker patients could have a lower albumin, b) protein nutrition deficiency, c) proteolysis occurring in critically ill patients and the negative protein balance. Hypoalbuminemia has also been found to be an independent risk factor for AKI in both randomized controlled trials and meta analyses.(62,63).

C. Co morbidities:

This study found that the presence of diabetes was a risk factor in development of AKI. Among co morbidities, chronic liver disease was also included, but as there were only 6 patients, it is underpowered to detect any association of significance. The finding that diabetics are at a higher risk of developing AKI fits in with the understanding that these patients already have a compromised renal function and diminished renal reserve hence the capacity to withstand another insult is limited. This predisposes these patients to higher chance

of developing AKI. Indian and Western centers, have found diabetes to be a significant factor to be commonly seen in association with AKI. (10,11, 15,28).

D. Risk factors

***i) Hypotension*:**

This study found that like earlier studies, hypotension was a significant factor in development of AKI (16,18). Most patients were having hypotension within the first 24 hours of admission and were found to have AKI on admission.

iii)Nephrotoxic drugs:

There was no association found between potentially nephrotoxic drugs used in the ICU and AKI in the univariate analysis of this study, though a few other studies done elsewhere have mentioned these as a common cause for AKI (27). The drugs commonly studied in these included NSAIDs, aminoglycosides, penicillins, amphotericin B and calcineurin inhibitors However, in this study ,the commonest drugs used were penicillins [broad spectrum like piperacillin tazobactam] and angiotensin converting enzyme receptors (ACEIs). Only two patients received Amphotericin B (26,64). NSAIDs and aminoglycosides were not used in the ICU. They are commonly identified in previous studies as risk factors for AKI (64). As part of a safe drug policy, aminoglycosides and NSAIDS are altogether avoided in the ICU. Thus the frequency of potentially nephrotoxic drugs used in ICU was not very high which can explain the low incidence of AKI noticed in our ICU. Also, the interstitial nephritis that is seen in penicillin use has been described as mainly idiosyncratic

which explains why even a high use of this class of drugs, was not a risk factor as per this study. In addition, as the early use of antibiotics would have taken care of the underlying sepsis, the factors leading to AKI would actually have improved thus actually leading to the confounding finding of low AKI in spite of such high beta lactams use. As these drugs comprised more than 95% of drugs used this could probably be the reason for low incidence of AKI in this group.

iii) Radiocontrast exposure:

There was significant development of contrast induced nephropathy in the univariate analysis but was not found to be significant on multivariate analysis. The reason for the low rate of contrast induced nephropathy could that as all of them had received adequate hydration prior to the procedure which would have reduced the incidence of the same in them. NAC was also used routinely for elective radiological procedures needing contrast.

***iv) Duration of mechanical ventilation*:**

Mechanical ventilation and its duration has been found to correlate with severity of AKI and its role in mortality according to studies (21,28). This study assessed the relation between these two factors and this study found no association between development of AKI and duration of ventilation. The reason could be that earlier studies looked for an association between mortality, AKI and duration of mechanical ventilation. The patients who were on ventilator for more than 15 days were 5; (3 had AKI while 2 did not), which could explain the reason why there was no significance, as the study was probably underpowered. A t-test was done to compare the means of duration of ventilation between the two groups (AKI vs non AKI) and found no statistical significance between the two. It could be possible that the sicker patients with AKI may have actually had a shorter duration of ventilation as they were very morbid on admission and may have deteriorated rapidly in the ICU, causing early

mortality, leading to a confounding factor while trying to study association between these two factors.

E. Scoring systems:

A significant finding was that of **a** higher APACHE II score in those with AKI. This can be explained on the basis of the fact that sicker patients are more likely to have renal failure. But there was no correlation between a second scoring system MODS and AKI. This was probably because APACHE II gives a more comprehensive analysis of the patients condition including more factors included in the calculation than MODS. As seen earlier, AKI is a component of multi organ dysfunction and can also be one of the risk factors responsible for the SIRS cascade seen in patients with multi organ dysfunction. The MODS scoring uses fewer criteria than APACHE 2 scoring and may not always be an accurate predictor for developing AKI as a more complete picture of the patient is better picked up in a detailed scoring system like the APACHE II scoring system.

F. Outcomes:

A sub analysis of the various classes of AKI, their incidence and association with mortality was done. The morbidity and mortality progressed as the class of AKI progressed on the R to E scale along with the necessity for dialysis. As patients were not followed up

after their discharge from ICU, patients could not be assessed for development of L (Loss) class in RIFLE.

There is definite correlation between class of AKI and mortality, need for RRT and an association of RRT with mortality.

Another important finding was the number of patients in the R and I classifications who would have been classified as "normal" under the old definition of renal failure, but were detected to have AKI under the new definition. Though the mortality was not significant in these patients, and none received RRT, the fact that they had developed AKI which would have been missed by the earlier definition was noticed.

LIMITATIONS

1. There were no patients who could be classified under the Loss (L) category in the RIFLE spectrum.

2. There were limited numbers of patients in some of the subgroups to do a statistical analysis.

CONCLUSIONS

In this cohort of patients admitted to the Medical ICU

1. A higher risk of developing AKI is found with advancing age, male gender, a higher APACHE II score at admission , hypoalbuminemia, bacterial infections, diabetes and hypotension.

2. The MODS score, liver diseases, tropical infections, the drugs used in the ICU, radiocontrast and other co morbidities were not associated with AKI.

3. A high RIFLE score is associated with a higher need for dialysis and a poorer outcome.

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APPENDIX I

Data abstraction form – Thesis

PATIENT SERIAL NUMBER:

Name:	Hospital Number:
Age:	Sex: State:
Occupation:	Length:

Diagnosis **Primary (reason for admission to ICU)**

Secondary (co morbidities) DM
Hypertension
IHD
Autoimmune
Others

Hospital DOA DOD
ICU DOA DOD
APACHE II MODS:
Outcome: Alive / Expired/DAMA /Withdrawal

Mechanical Ventilation Y/N Starting date Last date

Non Invasive ventilation Y/N Starting date Last date

Tracheostomy Y/N Date done

Antibiotic treatment

Name	Date of starting	Dose	Duration	Indication

Radiocontrast agents with dosage

Other nephrotoxic drugs

DRUG	**Date of initiation of drug**	**Date of stopping drug**	**Dosage**
Beta lactams			
Vancomycin			
Amphotericin			
Aminoglycosides			
NSAIDs			
Diuretics			
Acyclovir			
Mannitol			
Phenytoin			
ACEIs			
Others			

Nosocomial infections: VAP / UTI / CRBI / Others

Culture report:

Cardiac arrest prior to arrest and duration if CPR if patient had an arrest
Respiratory arrest prior to arrest

	D1	2	3	4	5	6	7	8	9	10
GCS										
Sedation										
Temp (max in Faren)										
HR >100/mt> 1 hr										
MAP< 70 >1hr										
Inotropes (Max)										
Inotropes (Min)										
Input										
Output										
Cumul balance										
Hb										
TC/DC										
Platelets										
PT/INR										
aPTT										
Na										
K										
Creat										
TB/DB										
Protein /albumin										
SGOT										
SGPT										
Alk. Phos										
Procal										
pH										
SpO2 (Max)										
SpO2 (Min)										
pCO2										
pO2										
HCO3-										
ABE										
Ventilation Mode										
FiO2 (Max)										
FiO2 (Min)										
PEEP (Max)										
PEEP (Min)										
RR (Max)										
RR (Min)										
TV (Max)										
TV (Min)										
PS										
CXR										
Adverse events if any										

CODES FOR MODE OF VENTILATION: 1- NIV 2-SIMV 3-PCV 4-CPAP

CODES FOR INOTROPES 1- Adrenaline 2- Noradrenaline 3- Dopamine 4- Vasopressin

SEROLOGY Leptospirosis
HIV
HBsAg
Scrub typhus
HCV
HAV
HEV

DIALYSIS DETAILS

	D1	2	3	4	5	6	7	8	9	10
Type										
Indication										
Duration										

CODES FOR DIALYSIS: 1- SLEDD
2- Intermittent hemodialys
3- Intermittent hemodiafiltration
4 - Intermittent ultrafiltration
5- Extended daily dialysis
6-Continuous therapies
7- Peritoneal dialysis
8- Continuous renal replacement therapies

CODES FOR INDICATIONS 1- Refractory Metabolic acidosis
2- Refractory hyperkalemia
3- Pulmonary edema/ ARDS
4- Uremic sgns and symptoms

Appendix II DATA MASTER SHEET

S.No	Pt In.	No	Age	Gender	Diag.	Co morbid	Scoring Systems APACHE 2	MODS	AKI	AKI	MV	GCS	Outcome
1	GE	535114d	35	0	2	0	23	5	1	2	1	10T	0
2	VS	504014d	24	1	0	0	19	5	1	1	0	15	0
3	UV	821178c	42	0	2	0	37	9	1	3	1	4T	1
4	VA	632428d	20	0	0	0	37	10	1	1	1	2T	3
5	SA	328935d	49	0	0	0	35	10	1	1	1	2T	1
6	CR	461512d	50	1	0	1	25	2	1	5	0	15	3
7	VE	597204d	35	1	1	0	34	12	1	1	1	2T	0
8	PE	603076d	81	1	1	1	36	6	1	1	1	2T	0
9	DB	535359d	61	1	1	1	24	4	1	1	1	15	0
10	JL	632306d	39	0	0	0	15	6	0	0	0	15	0
11	SM	828284c	69	1	2	5	35	8	0	0	0	15	0
12	MP	589613d	61	0	2	7	26	8	0	0	1	2T	1
13	LV	605745d	21	0	0	0	20	8	0	0	0	12	0
14	VA	507671c	84	0	1	0	26	11	0	0	0	8	0
15	JL	156098a	69	0	0	9	24	9	0	0	1	2T	1
16	VV	595896d	56	1	0	2	14	6	1	1	1	2T	1
17	SA	244862d	62	0	0	3	21	6	0	0	1	2T	0
18	PM	613358d	45	1	0	0	14	10	0	0	1	2T	0
19	MA	554350d	76	0	0	0	26	9	1	3	1	2T	0
20	KS	530171d	45	1	1	2	34	8	1	3	1	2T	1
21	V	603214d	26	0	1	0	31	12	0	0	1	2T	4
22	JS	587671c	84	0	2	2	25	8	0	0	0	14	0
23	SA	638327d	16	0	0	5	10	8	1	1	0	15	0
24	AB	603567d	68	0	1	0	28	8	0	0	0	10	0
25	LA	036472c	74	0	0	1	36	9	1	1	1	2T	1
26	PA	433985d	33	1	2	0	29	14	1	1	1	2T	1
27	LA	582380d	65	0	0	1	32	5	1	1	1	2T	0
28	HA	856487c	58	1	0	7	25	6	1	1	0	15	0
29	VA	559260d	30	0	1	0	26	7	1	1	1	12	0

Codes:::: DIAGNOSIS: 0- Non infectious, 1- Non tropical bacterial infections, 2- Tropical infections, 3-Liver diseases
COMORBIDITIES: 0- None, 1- Diabetes, 2- Hypertension, 3- Ischemic heart disease, 5- Chronic Kidney Disease, 6- Chronic Liver disease, 7- Connective tissue disorder, 8- Malignancies,

S.No	In.	No	Age	Gender	Diag.	Co morbid	Scoring systems		AKI	AKI Class	M V	GCS	Outcome
							APACHE	MODS					
30	SP	512637d	25	0	1	7	39	11	0	0	1	5T	1
31	RA	838895b	68	1	1	7	35	8	1	3	1	2T	0
32	PL	587629d	44	0	1	0	13	6	1	3	0	15	0
33	BS	601817d	61	1	2	1	33	11	0	0	1	2T	0
34	SA	559269d	30	0	0	0	26	12	0	0	1	6T	0
35	MO	850478c	58	1	1	7	25	6	1	1	0	15	0
36	DN	472291d	44	1	1	2	13	8	0	0	0	10T	0
37	PA	472009d	16	1	1	0	7	2	0	0	1	10T	0
38	JA	540188d	61	1	0	9	33	9	0	0	1	2T	0
39	MA	535461d	35	0	0	0	17	11	0	0	1	15	0
40	VR	544553d	17	1	0	0	24	9	0	0	1	2T	0
41	GA	543674d	19	0	2	0	33	10	1	1	1	2T	3
42	SA	559231d	18	0	3	0	10	2	0	2	0	15	1
43	RA	518129d	35	1	2	0	16	9	0	0	0	15	0
44	DL	518041d	21	0	2	0	24	10	0	0	0	15	0
45	JR	244872c	62	0	2	3	21	6	0	0	1	2T	0
46	KK	474154d	36	0	0	0	19	4	0	0	0	14	0
47	GE	302816d	18	0	0	0	32	7	0	0	1	2T	1
48	BR	472280d	24	1	0	0	17	10	0	0	1	2T	3
49	RA	569269d	30	0	0	0	19	6	0	0	1	6T	0
50	CS	561641d	53	0	0	0	20	8	0	0	0	15	0
51	SA	549328d	25	0	0	0	11	3	0	0	0	15	0
52	SR	108718c	41	1	2	0	22	9	0	0	0	15	0
53	AM	563777d	28	0	2	0	16	5	1	2	1	15	0
54	GE	600067d	39	0	2	0	18	4	0	0	1	2T	0
56	GE	563474d	19	0	1	0	28	8	1	0	1	2T	3
57	SA	608550d	70	0	3	8	41	13	1	1	1	2T	0
58	LB	613160d	75	0	1	1	48	12	1	5	1	2T	1
59	CA	613347d	75	0	1	1	27	8	1	1	0	15	0
60	PA	644333d	32	1	1	0	30	9	1	3	1	7	0

Codes:::: DIAGNOSIS: 0- Non infectious, 1- Non tropical bacterial infections, 2- Tropical infections, 3-Liver diseases
COMORBIDITIES: 0- None, 1- Diabetes, 2- Hypertension, 3- Ischemic heart disease, 5- Chronic Kidney Disease, 6- Chronic Liver disease, 7- Connective tissue disorder, 8- Malignancies, 9- Miscellaneous

S.No	Pt In.	No	Age	Gender	Diag.	Co morbid	Scoring Systems	AKI		AKI Class	MV		GCS	Outcome	
61	GS	630498d	53	1	0	1	21	10	1		3	1	15	0	
62	MA	554350d	76	0	0	0	26	9	1		3	1	2T	0	
63	BA	591006d	50	1	2	0	43	15	1		3	1	2T	1	
64	MR	563407d	53	1	1	1	32	5	1		1	1	2T	0	
65	JR	608199d	65	0	0	1	43	13	1		1	1	2T	1	
66	DA	638554d	39	1	0	1	33	11	1		3	1	4T	1	
67	NJ	497807d	45	1	1	1	40	13	1		1	1	3	1	
68	RS	535388d	54	1	1	7	21	16	1		2	1	2T	1	
69	VL	599401d	19	0	1	0	17	8	1		1	1	15	0	
70	SA	672485a	80	0	2	1	36	8	1		2	0	11	1	
71	MO	608599d	55	1	1	2	34	13	1		2	1	3	0	
72	BV	699293b	73	1	1	2	36	10	1		2	0	2T	1	
73	SH	033047d	63	1	1	2	39	7	1		1	0	3	0	
74	MH	330130b	90	1	0	0	34	6	1		2	0	3	0	
75	RB	190357d	60	1	0	1	27	5	1		2	0	15	0	
76	PA	330130c	75	0	1	1	48	12	1		5	1	2T	1	
77	RA	644152d	15	1	1	0	22	10	1		2	1	15	0	
78	KA	645722d	68	0	2	1	27	6	1		3	0	15	0	
79	RA	5938580d	40	0	0	7	17	8	1		5	1	15	1	
80	AB	392672d	55	0	1	1	26	6	1		3	1	3	1	
81	SU	596620d	57	1	1	1	40	7	1		3	0	3	0	
82	JE	604149d	45	1	1	1	40	13	1		3	0	3	1	
83	KP	603059d	35	0	3	0	37	11	1		1	0	3	1	
84	KM	305073c	61	0	0	4	28	7	1		5	1	15	0	
85	NN	597298d	33	0	0	0	44	13	1		3	1	2T	0	
86	ZO	405991a	47	0	0	7	38	9	1		2	0	2T	1	
87	FB	535355d	65	1	0	1	36	8	1		3	0	15	1	
88	SB	593580d	40	1	0	0	28	14	1		3	0	15	1	
89	MR	569598d	45	1	0	5	17	13	1		3	1	3	1	
90	JO	159208	70	1	3	2	22	5	1		5	1	15	0	
91	CN	763636d	63	0	0	2	30	4	1		2	0	15	0	
92	JA	620556d	21	1	2	0	33	13	1		2	1	2T	0	
93	MA	554350d	76	0	0	0	26	9	1		3	1	2T	0	
94	VE	213832c	74	1	1	3	13	6	1		1	3	15	0	

Codes:::: DIAGNOSIS: 0- Non infectious, 1- Non tropical bacterial infections, 2- Tropical infections, 3-Liver diseases
COMORBIDITIES: 0- None, 1- Diabetes, 2- Hypertension, 3- Ischemic heart disease, 5- Chronic Kidney Disease, 6- Chronic Liver disease, 7- Connective tissue disorder, 8-malignancies

S.No	Pt In.	No	Age	Gender	Diag.	Co morbid	Scoring Systems		AKI	AKI Class		MV	GCS	Outcome
							APACHE	MODS						
95	ML	630103d	40	1	0	0	13	6	1	3	0	15	0	
96	SR	472037d	42	1	2	0	16	10	1	3	1	15	0	
97	VA	556816d	25	0	2	0	13	5	1	1	1	15	0	
98	SI	630008d	35	0	2	0	13	7	1	2	0	15	0	
99	ML	630131d	38	0	2	0	26	9	1	3	0	10T	0	
100	JS	577164d	36	1	2	0	21	7	1	3	0	15	1	
101	LN	548449d	51	0	1	0	40	13	1	1	0	2T	1	
102	EP	535147d	53	1	2	1	46	11	1	3	0	2T	1	
103	NE	325977d	25	1	0	0	24	8	1	1	0	6T	0	
104	RE	528848d	57	1	0	7	25	10	1	3	0	15	0	
105	JK	469607d	28	1	0	0	28	13	1	2	1	4T	0	
106	KC	476626d	42	0	0	8	11	6	1	2	0	15	0	
107	SR	624619d	49	1	1	8	18	5	1	2	0	15	0	
108	CH	654402d	51	0	0	1	41	7	1	3	1	2T	0	
109	RO	469554d	23	1	1	1	35	11	1	5	1	6T	1	
110	SS	475844d	30	1	0	0	20	8	1	2	1	15	1	
111	KS	554210d	34	1	0	0	29	11	1	1	1	5T	2	
112	SM	472278d	40	1	0	1	24	7	1	3	1	10T	0	
113	RA	541556d	56	1	1	7	26	14	1	3	0	15	1	
114	SS	401589d	38	1	1	7	14	8	1	1	1	15	4	
115	PA	578208d	55	0	1	0	18	10	1	3	0	15	0	
116	SA	465858d	62	1	2	9	19	6	1	3	0	15	3	
117	RA	440932b	64	0	0	1	20	6	1	3	0	15	1	
118	GA	530448d	18	1	1	0	29	7	1	3	1	2T	1	
119	PR	620033d	51	1	0	1	39	13	1	3	1	3	0	
120	KS	603076d	81	1	1	9	23	9	1	1	1	2T	0	
121	GA	597182d	25	0	1	7	33	9	1	2	1	2T	0	
122	SM	607810d	39	1	1	8	28	11	1	1	0	15	3	
123	AM	461695d	30	1	1	0	11	7	1	3	1	4T	1	
124	MA	554350d	76	0	0	0	26	9	1	3	1	2T	0	
125	PM	306747c	73	0	2	0	37	8	1	1	1	2T	0	

Codes:::: DIAGNOSIS: 0- Non infectious, 1- Non tropical bacterial infections, 2- Tropical infections, 3-Liver diseases
COMORBIDITIES: 0- None, 1- Diabetes, 2- Hypertension, 3- Ischemic heart disease, 5- Chronic Kidney Disease, 6- Chronic Liver disease, 7- Connective tissue disorder, 8-malignancies

S.No	Pt In.	No	Age	Gender	Diag.	Co morbid	Scoring Systems	AKI	AKI Class	MV		GCS	Outcome	
126	RA	470378d	60	1	0	0	27	6	1		1	1	15	0
127	SA	550527C	25	0	0	0	12	4	0		0	0	15	0
128	PA	563919d	45	1	0	0	32	11	1		1	1	2T	0
129	SU	603246d	39	0	2	0	33	8	1		2	1	2T	1
130	BH	306747c	73	0	0	3	27	6	1		1	1	2T	0
131	KD	434410d	44	1	0	5	37	12	1		3	1	2T	2
132	VL	608377d	38	0	1	7	27	7	1		2	1	2T	0
133	MO	608599d	55	1	1	0	34	13	1		2	1	3	0
134	MA	605729d	24	0	2	1	26	9	1		1	1	2T	1
135	RK	597182d	25	0	2	7	33	9	1		2	1	2T	0
136	LA	577052d	40	0	1	0	29	6	1		1	0	5T	0
137	VK	597412d	54	1	0	0	18	9	1		1	1	15	2
138	SB	540268d	20	0	2	0	26	13	1		1	1	15	0
139	KO	653370d	28	0	0	0	22	9	0		0	1	2T	0
140	PA	549323d	25	0	0	0	11	3	1		1	0	15	0
141	DN	530134d	46	1	0	1	26	8	1		2	1	4T	0
142	JE	644333d	32	0	0	1	34	14	1		5	1	2t	1
143	MS	236835b	52	1	0	8	29	11	1		3	1	7	1
144	TA	476644d	54	0	1	8	29	11	0		0	1	8	0
145	SK	593994d	24	1	1	1	18	8	1		3	0	3T	1
146	BS	5277556d	49	1	0	6	29	11	0		0	1	3	1

Codes:::: DIAGNOSIS: 0- Non infectious, 1- Non tropical bacterial infections, 2- Tropical infections, 3-Liver diseases
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Appendix III

APACHE II SCORE

Total Acute Physiology Score (APS) Sum of the individual 12 points = A
Total APACHE 2 score = Sum of A (APS) +B (age)+ C (chronic health points)

C= Chronic health points

- Elective post op +2 pts
- Non operative or emergency post op +5 pts
- If any of the below is yes give +5 pts: 1) cirrhosis with portal hypertension or hepatic encephalopathy 2) class IV angina at rest 3) chronic hypoxemia, hypercapnia or polycythemia 4) chronic peritoneal or hemodilaysis 5) Immunocompromised host

	HIGH ABNORMAL					LOW ABNORMAL			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (rectal)	>41	30-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	<29.9
MAP= (2xdaistolic+ systolic)/3	>160	130-159	110-129		70-109		50-69	40-54	<49
Heart rate	>180	140-179	110-139		70-109		55-69	40-54	<39
Respiratory rate	>50	35-49		25-34	12-24	10-11	6-9		<5
Oxygenation **a) FiO2>0.5 then A-aDO2** **b) FiO2<0.5 then PaO2**	>500	350-499	200-349		<200 PO2 >70	PO2 61-70		pO2 55-60	pO2 <55
Arterial pH/serum bicarb if no ABG avail.	>7.7/>52	7.6-7.69/ 41-51.9		7.5-7.59/ 32-40.9	7.33-7.49/ 22.31.9		7.25-7.32/ 18-21.9	7.15-7.24/ 15-17.9	<7.15 / <15
Na	>180	160-179	155-159	150-154	130-149		120-129	111-119	<110
K	>7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Creat	>3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit	>60		50-59.9	46-49.9	30-45.9		20-29.9		<20
WBC count	>40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GCS **(15-actual GCS)= The Score**									

Age points (years): <44=0, 45-54= 2, 55-64= 3, 65 to 74= 4, > 75 = 5.

MODS scoring

	0	1	2	3	4
Respiratory (P/F ratio)	>300	226-300	151-225	76-150	<75
Hematological (platelets x 1000)	>120	81-120	51-80	21-50	<20
Hepatic (bili mg/dl)	<1.2	1.2-3.5	3.5-7	7-14	>14
CVS (HRxCVP/MAP)	<10	10.1-15	15.1-20	20.1-30	>30
GCS	15	13-14	10-12	7-9	<6
Renal (mg/dl)	<1.1	1.2-2.3	2.3-4	4-5.7	>5.7